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The role of underlying nephropathy in the progression of renal disease

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The role of underlying nephropathy in the progression of renal disease.

Background. Disease-specific pathogenic mechanisms may be major determinants of the spontaneous rate of progression of chronic renal failure (CRF). To clarify the role of different underlying renal diseases, we examined the rate of CRF progression in 886 patients with chronic nephropathies.

Methods. Secondary analysis of two multicenter, prospective randomized trials: the Northern Italian Cooperative study (NIC) and the AIPRI study (ACE-Inhibition in Progressive Renal Insufficiency). Univariate and multivariate analyses of variance were used to select the covariates possibly related to CRF progression (estimated by means of the slope of the reciprocal of S_{Cr} against time), focusing on the contributory role of primary renal diseases.

Results. The overall rate of CRF progression was relatively low but there was a considerable difference in the slopes relating to the underlying nephropathy (particularly evident in the patients with chronic glomerulonephritis (CGN)). The median rate of CRF progression in both studies was more rapid in patients with polycystic kidney disease (PKD) and CGN than in those with other nephropathies. Multivariate analysis showed PKD as an independent predictor of the CRF progression rate only in the NIC Study ($P < 0.0015$); the selected variables in both studies predicted a variation of only 15–18% in the CRF progression rate.

Conclusion. The underlying renal disease certainly plays a role in the natural history of CRF, but the variability of the CRF progression rates related to different renal diseases and between individuals with the same diagnosis underlines the need for caution in evaluating risk factors and predicting single patient outcomes.

Although chronic renal failure (CRF) progresses towards end-stage renal disease (ESRD) in the majority of cases, the rate of the decline in glomerular filtration rate (GFR) varies in groups of patients with different nephropathies, and also in patients with the same disease. A number of physiological and metabolic changes may contribute towards progressive renal destruction, and various intercurrent events may accelerate the deterioration of renal function; however, the fact that the underlying nephropathy is probably the major determinant of the spontaneous rate of progression suggests the existence of a disease-specific pathogenic mechanism.

A number of clinical studies designed to evaluate the factors involved in the progression of CRF have shown that the underlying disease is one of the factors determining the natural history of CRF [1–9], but the published results are equivocal, mainly because most involved small and very heterogeneous populations and the data were collected retrospectively. Furthermore, they usually considered only the crude cumulative renal survival of the different nephropathies (without taking into account concomitant risk factors), and the fact that the rate of the decline in GFR was measured using different methods further complicates any comparison.

With the aim of clarifying the role of the underlying renal disease on CRF progression, we examined the changes in renal function over time in two large cohorts of patients with chronic renal disease of different causes and severity enrolled in two multicenter, prospective randomized trials designed to clarify the role of protein restriction [10] and the administration of an ACE inhibitor [11] in delaying CRF progression.

METHODS

The study was based on the secondary analysis of the individual data contained in the databases of two large-scale clinical trials [10, 11] involving CRF patients with various renal diseases.

Patients

The Northern Italian Cooperative (NIC) study [10] was a 2-year, multicenter, randomized, prospective trial designed to determine the effectiveness of dietary protein restriction (0.6 versus 1 g protein/kg ideal body weight/day) on the progression of renal disease in 456 patients with CRF. The Angiotensin-Converting-Enzyme Inhibition

Key words: chronic renal failure, progression, underlying renal disease, proteinuria, hypertension

Table 1. Baseline characteristics of the NIC and AIPRI patients by renal diagnosis

	CGN	HNS	CIN	PKD	DN	Other	Total
NIC study							
N [% of total]	117 [28.3%]	64 [15.5%]	144 [34.7%]	69 [16.7%]	—	20 [4.8%]	414 [100%]
Age, *years**	43 ± 11	54 ± 7	50 ± 11	47 ± 9	—	48 ± 13	48 ± 11
Gender, *male* (%)	56	66	47	55	—	55	54
S_{Cr}, *mg/dL**	3.02 ± 1.22	2.77 ± 1.10	2.92 ± 1.35	3.41 ± 1.60	—	3.29 ± 1.39	3.02 ± 1.34
Hb, *g/dL**	13.3 ± 1.9	13.5 ± 1.5	13.4 ± 2.1	13.1 ± 1.8	—	12.9 ± 2.1	13.3 ± 1.9
Systolic BP, *mm Hg**	146 ± 22	158 ± 22	150 ± 23	151 ± 20	—	151 ± 17	150 ± 22
Diastolic BP, *mm Hg**	94 ± 12	96 ± 11	94 ± 13	96 ± 13	—	94 ± 11	95 ± 12
Mean BP, *mm Hg**	111 ± 14	117 ± 13	113 ± 15	114 ± 14	—	113 ± 12	113 ± 14
Proteinuria, *g/day*†	1.3	0.4	0.5	0.1	—	1.3	0.5
(25^{th}–75^{th} percentile)	(0.5–2.3)	(0.0–0.9)	(0.1–1.2)	(0.0–0.6)	—	(0.3–2.1)	(0.1–1.5)
AIPRI study							
N [% of total]	170 [36.0%]	99 [21.0%]	90 [19.1%]	57 [12.1%]	19 [4.0%]	37 [7.8%]	472 [100%]
Age, *years*	48 ± 12	60 ± 8	53 ± 13	48 ± 9	59 ± 9	53 ± 12	52 ± 12
Gender, *male* (%)	73	72	62	74	84	78	72
S_{Cr}, *mg/dL*	2.16 ± 0.60	1.85 ± 0.38	2.10 ± 0.70	2.31 ± 0.71	2.40 ± 0.73	2.18 ± 0.66	2.11 ± 0.63
Hemoglobin, *g/dL*	13.6 ± 1.6	14.0 ± 1.5	13.8 ± 1.7	13.5 ± 1.5	12.9 ± 1.6	13.7 ± 1.6	13.7 ± 1.6
Systolic BP, *mm Hg**	143 ± 14	150 ± 16	143 ± 15	144 ± 17	155 ± 15	145 ± 16	145 ± 16
Diastolic BP, *mm Hg**	90 ± 7	88 ± 8	89 ± 7	92 ± 7	86 ± 6	90 ± 7	89 ± 7
Mean BP, *mm Hg**	108 ± 8	108 ± 9	107 ± 8	109 ± 9	109 ± 7	108 ± 9	108 ± 9
Proteinuria, *g/day*†	1.9	0.3	0.7	0.3	3.4	0.8	0.9
(24^{th}–75^{th} percentile)	(0.7–4.0)	(0.0–0.8)	(0.1–2.1)	(0.1–1.1)	(1.9–7.1)	(0.2–3.0)	(0.2–2.6)

Abbreviations are: BP, blood pressure; Hb, hemoglobin; S_{Cr}, serum creatinine.
* Values expressed as mean ± SD
† Values expressed as median

in Progressive Renal Insufficiency (AIPRI) study [11] was a 3-year, multicenter, prospective, double-blind, randomized trial designed to determine the effect of the ACE inhibitor benazepril on the progression of CRF in 583 patients with various underlying renal diseases. The study designs and their inclusion and exclusion criteria have been reported in detail elsewhere [10, 11]. In both studies, the patients were stratified on the basis of renal function: those enrolled in the NIC Study were divided into three groups according to their baseline serum creatinine (S_{Cr}): group A (S_{Cr} 1.50–2.50 mg/dL); group B (S_{Cr} 2.51–5.00 mg/dL); group C (S_{Cr} 5.01–7.00 mg/dL); the AIPRI population was divided into two groups according to their baseline creatinine clearance (C_{Cr}) calculated according to Cockcroft's formula (mild CRF: C_{Cr} 46–60 mL/min; moderate CRF: C_{Cr} 30–45 mL/min).

The cause of the renal disease was determined in each patient on the basis of their medical history and the results of a physical examination, urinalysis, biochemical tests, and radiological and ultrasonographic studies; most of the patients with proteinuria also underwent renal biopsy. All of the diagnoses were confirmed by a Quality-Control and End-point Evaluation Committee.

Statistical analysis

The individual data were used to calculate the individual patient slopes of the reciprocal of S_{Cr} versus time, which was subsequently used to test the effect on CRF progression of the underlying renal disease and some baseline and follow-up clinical covariates. Percentile distribution (with the median as central tendency statistic and 25th and 75th percentile values as variability indices) was used for continuous non-normally distributed variables. Univariate analysis of variance was used as the first step to select the potential covariates possibly related to CRF progression, estimated by means of the slope of the reciprocal of S_{Cr} versus time, which was considered the main response variable. The two databases were analyzed separately (see Appendix 1 for the list of tested covariates), and the variables with a significance of ≤ 0.1 were then included in the multivariate analysis based on the general linear model of the analysis of variance for two parallel groups with three (NIC) or two (AIPRI) strata of CRF severity. The controlled-protein diet in the NIC study patients, and the placebo group of the AIPRI study, were used as standard treatments. The proteinuria data underwent natural logarithm transformation because of their right skewed distribution (for the purposes of calculation, all zero values were considered equivalent to 0.01 g/day). The assumption of the normality of the error term required by this model was tested using the analysis of residuals. A probability value of less than 0.05 was considered statistically significant. The statistical analyses were made using SPSS for Windows, Release 9.0.

RESULTS

Baseline characteristics

From a total of 1039 patients (456 NIC and 583 AIPRI patients), we selected the 886 patients (414 NIC and 472 AIPRI) for whom at least three post-randomization S_{Cr} measurements were available; their baseline characteristics and the causes of CRF are summarized in Table 1.

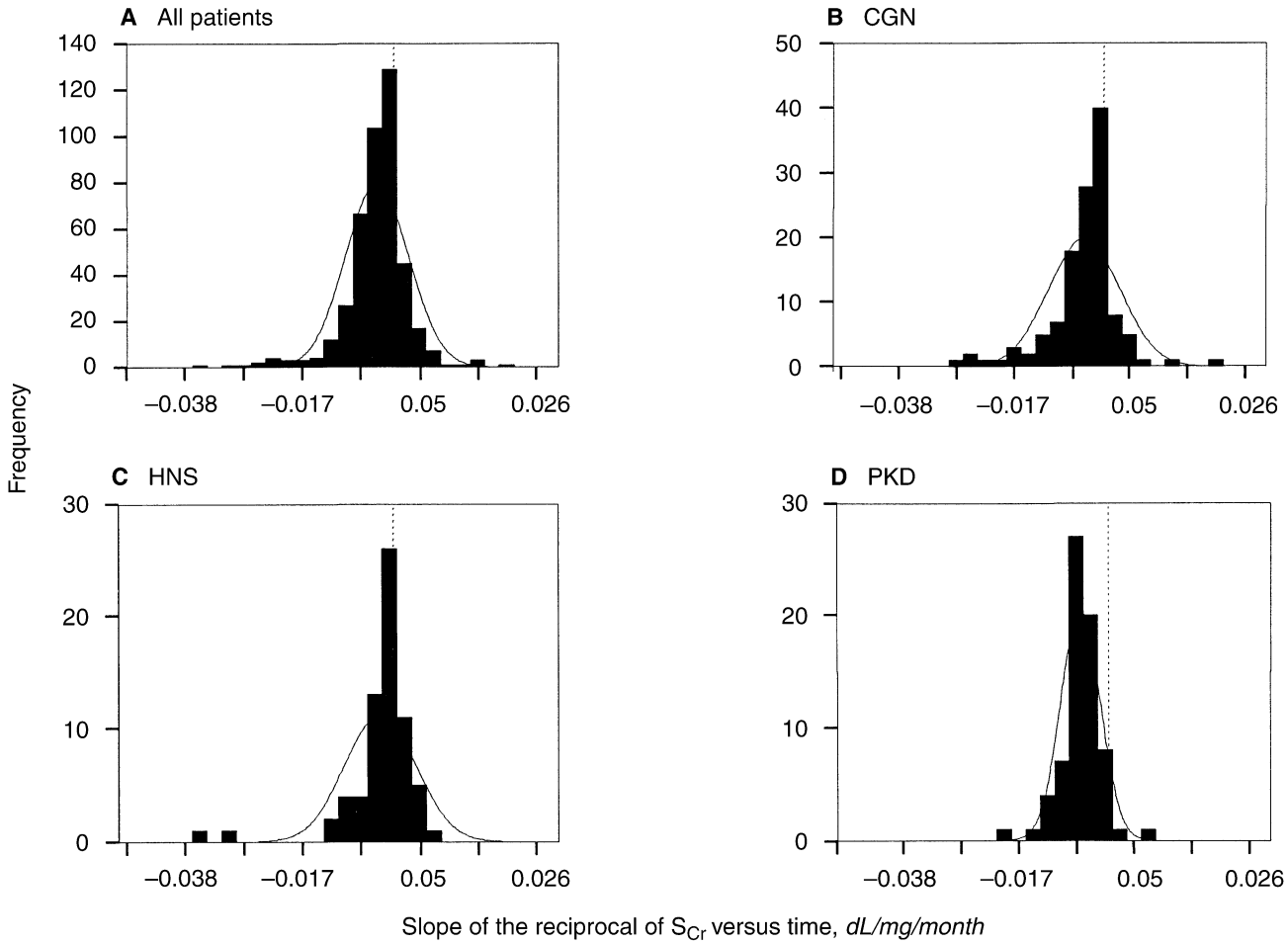

Fig. 1. Frequency distribution of the slopes of the reciprocal of S_{Cr} versus time in the NIC study [10] overall and according to renal disease.

Baseline renal function was better in the AIPRI than in the NIC study (S_{Cr} 2.11 ± 0.62 mg/dL versus 3.04 ± 1.36 mg/dL), but median proteinuria was higher (0.9 versus 0.6 g/day) and its greater interquartile range (2.4 versus 1.4 g/day) suggested a higher degree of variability. Mean blood pressure was lower in the AIPRI study (108 ± 9 mm Hg versus 113 ± 14 mm Hg).

Rate of CRF progression

Figure 1 and Figure 2 show the distribution of the linear slopes of the reciprocal of S_{Cr} in the two groups: in both studies, neither the overall slopes nor those of the groups of patients defined by the underlying renal disease were normally distributed. In the chronic glomerulonephritis (CGN) groups, kurtosis (the statistic describing the distribution pattern) was always higher and the distribution was skewed to the left, thus suggesting their heterogeneous nature. Slope variability was greater in the CGN groups than in those with polycystic kidney disease (PKD), as can also be seen in Fig. 3 in which the slopes are shown by renal diagnosis using the boxplot technique: the height of the box (which represents the interquartile range) is greater in the former than the latter. In both studies, the patients with CGN and PKD showed a faster rate of CRF progression (the boxes are below the zero reference line, which indicates no progression in renal disease). Progression was fastest in the patients with diabetic nephropathy (DN), but these were few in number and restricted to the AIPRI study.

The percentile distribution of the slopes in the two studies (overall and by underlying renal disease) are shown in Table 2. The median overall slopes were −0.027 dL/mg/year in the NIC and −0.029 dL/mg/year in the AIPRI study. The 75th percentile values were, respectively, −0.001 and −0.002 dL/mg/year, which means that the loss of renal function in 25% of the patients was less than 0.1% and 0.2%, and/or that some even had a positive slope (i.e., a gain in renal function over time). The percentages of patients with each underlying renal disease who had a positive slope during follow-up are shown in Table 2. In the groups of patients with hypertensive nephroangiosclerosis (HNS) and chronic interstitial nephritis (CIN) of both studies these percentages were strikingly high (39% and 30% in the HNS and CIN

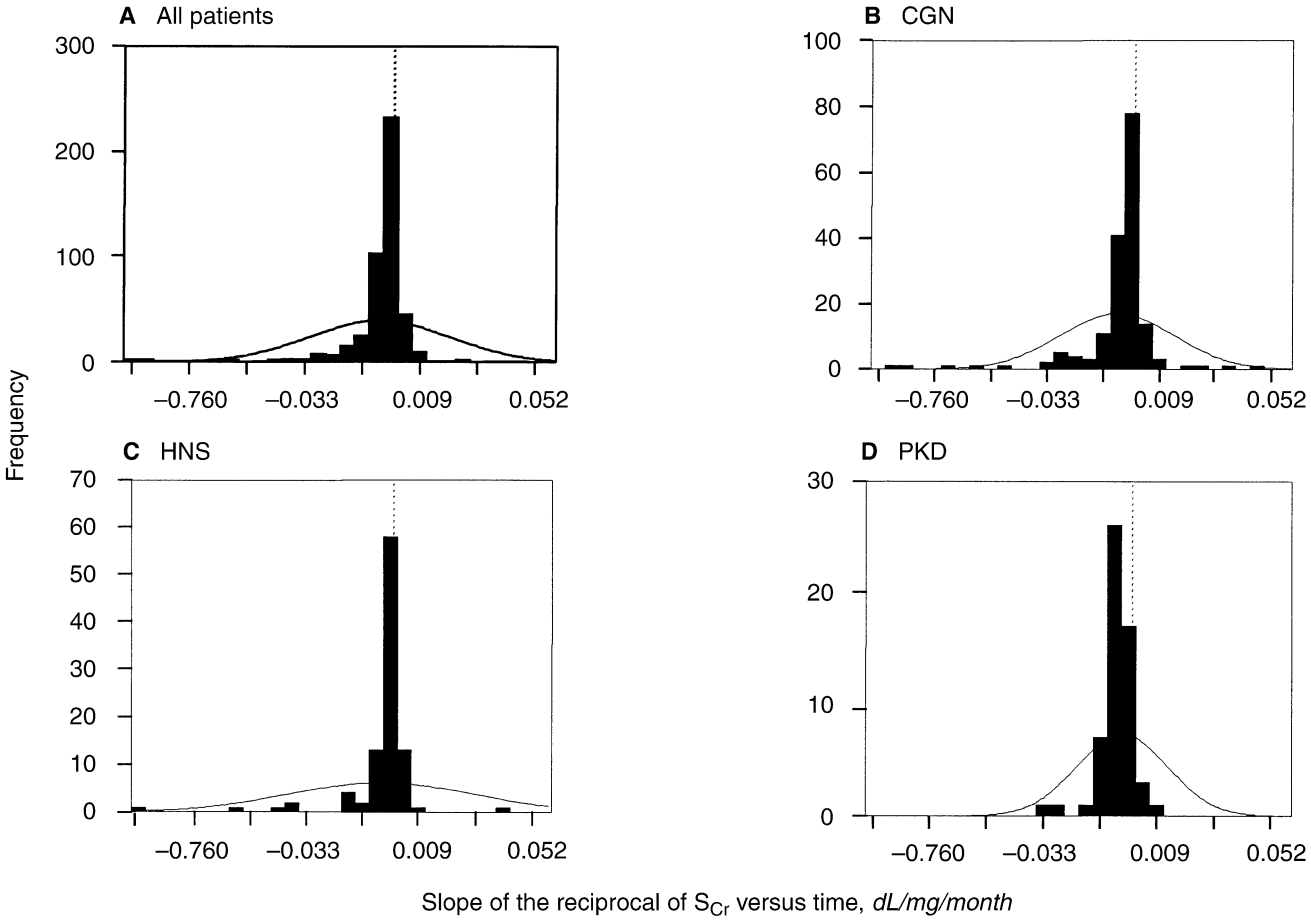

Fig. 2. Frequency distribution of the slopes of the reciprocal of S_{Cr} versus time in the AIPRI study [11] overall and according to renal disease.

groups of the NIC study; 31% and 29% in the HNS and CIN groups of the AIPRI study); on the contrary they were much lower in the PKD groups (3% and 12% in the NIC and AIPRI studies, respectively). Conversely, the loss of renal function in another 25% of patients was, respectively, 6.3% and 8.0%, which means that despite relatively low progression rate observed in the overall populations, a considerable number of the patients in both studies experienced a clinically relevant annual loss of renal function per year, with the fastest progression being observed in the lowest 5th percentile distribution of the AIPRI study (33.4%). When considering the rate of progression by underlying renal disease (Table 2), we found that the patients with PKD, DN or (to a lesser extent) CGN showed a specific and worse pattern than the population as a whole, with the PKD patients having the worst distribution (median and 25th percentile of −0.059 and −0.081 versus −0.027 and −0.063 in the NIC study; −0.062 and −0.094 versus −0.029 and −0.080 dL/mg/year in the AIPRI study). In the AIPRI study, DN patients also had a much worse distribution than the population as a whole (median and 25th percentile of −0.064 and −0.167 versus −0.029 and −0.080).

Multivariate analysis

At univariate analysis, a number of covariates related to the slope of the reciprocal of S_{Cr} over time in both studies (see Appendix 1).

In the NIC study, age and the duration of follow-up were positively related to the slope ($P < 0.0062$ and $P < 0.0001$, respectively), whereas high systolic blood pressure ($P < 0.0435$), a high degree of proteinuria (in the log scale) ($P < 0.0022$) and PKD (in comparison with non PKD) ($P < 0.0015$) were associated with a faster rate of progression. The contributory role of PKD was greatest in the patients with mild CRF at baseline (stratum A), with a more than 5% absolute difference in the annual loss of renal function; it was less in the intermediate stratum and complete absent in stratum C, in which baseline renal function was greatly compromised ($S_{Cr} > 5$ mg/dL) (Fig. 4). Overall, this model explained 18% of the slope variability.

In the AIPRI study, the slope of the reciprocal of S_{Cr} versus time significantly correlated with baseline renal function (a better slope for the patients with mild CRF; $P < 0.0005$), mean follow-up proteinuria (in the log-

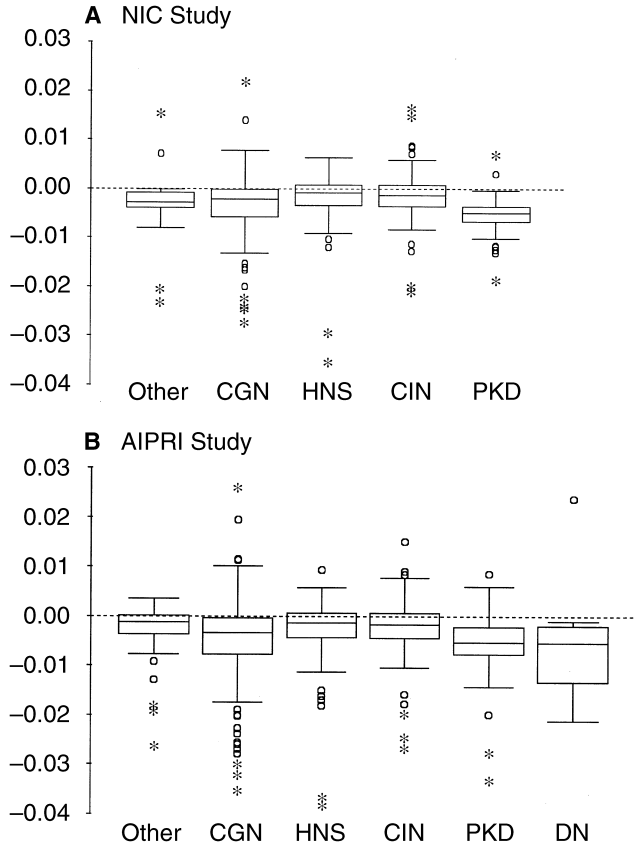

Fig. 3. Slopes of the reciprocal of S_{Cr} versus time by renal diagnosis represented with the technique of the box-plots in the NIC [10] and AIPRI [11] studies. The zero reference line indicates no progression of the renal disease; the height of the box represents the interquartile range.

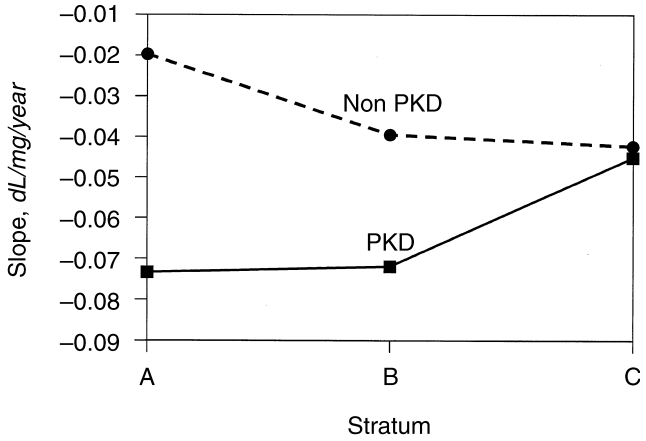

Fig. 4. Representation of the contributory role of PKD at multivariate analysis according to baseline renal function in the NIC study [10]. The effect of the diagnosis of PKD was more relevant in patients with mild CRF at baseline (Stratum A), lower in the intermediate stratum and absent in the patients with heavy compromised renal function (Stratum C).

scale) ($P < 0.0001$), and the standard error of the slope ($P < 0.0001$). These two last covariates were negatively related to the slope, with the higher values being associated with a more negative slope. There was also a significant interaction affecting slope prediction between mean proteinuria and mean diastolic blood pressure during follow-up ($P < 0.0001$). A diagnosis of PKD did not independently contribute to the rate of CRF progression. This model explained 15% of the slope variability.

DISCUSSION

Assessing the rate of CRF progression is useful not only for prognostic purposes, but also for establishing the effect of therapy on the natural history of renal disease; it is therefore crucial to acquire a greater understanding of the natural history of CRF, the underlying nephropathies and the factors influencing their progression. This is why we wanted to analyze the rate of CRF progression in a very large number of patients followed prospectively with serial determinations of renal function over time, with the aim of better clarifying the contributory role of the underlying renal disease in the natural history of CRF.

The results confirm that the underlying disease is associated with the rate of CRF progression. In both studies, the groups of patients with PKD and CGN experienced a faster mean rate of CRF progression in comparison with the other groups, although the small group of NIDDM patients with DN in the AIPRI study also had a fast CRF progression rate. Multivariate analysis showed that PKD was an independent predictor of the rate of CRF progression only in the NIC study; other analyses of cumulative renal survival in the same samples have shown that PKD patients also have the highest probability of reaching the end-points of a doubling in baseline S_{Cr} or the need for dialysis [11–13].

The Modification of Diet in Renal Disease (MDRD) study [8] likewise found that PKD was the most progressive chronic renal disease: in the PKD patients with moderate CRF, the mean rate of CRF progression (estimated as the slope of GFR measured using the renal clearance of ^{125}I-iothalamate) was 3.56 mL/min/year faster than in the patients with CGN or other nephropathies, although it was only 1.59 mL/min/year faster in the PKD patients with more advanced CRF. This is in line with our observation that the predictivity of a PKD diagnosis as an independent marker of CRF progression decreases with the greater severity of baseline CRF (Fig. 4). The rate of progression of PKD observed in the MDRD study [8] was similar to that observed by Jungers et al [6], who found a lower rate of progression in PKD than in CGN patients probably because of a selection bias towards the more progressive forms of renal disease occurring in this retrospective study; other smaller and/or retrospective studies have reported a lower rate of progression in CIN and PKD patients than in those with CGN or HNS [3, 4].

The greater contributory role of PKD in CRF progres-

Table 2. Percentile distribution of the slope of the reciprocal of S_{Cr} versus time in the NIC and AIPRI studies by renal diagnosis

	CGN	HNS	CIN	PKD	DN	Other	Total
NIC Study							
Positive slope							
N	22/117 (19%)	25/64 (39%)	43/144 (30%)	2/69 (3%)	—	1/20 (5%)	93/414 (23%)
Slope, *dL/mg/year*							
95 percentile	0.052	0.047	0.068	−0.006	—	0.167	0.048
75 percentile	−0.003	0.009	0.009	−0.042	—	−0.010	−0.001
Median	−0.026	−0.010	−0.015	−0.059	—	−0.033	−0.027
25 percentile	−0.070	−0.042	−0.044	−0.081	—	−0.048	−0.063
5 percentile	−0.199	−0.134	−0.098	−0.144	—	−0.274	−0.144
AIPRI Study							
Positive slope							
N	36/170 (21%)	31/99 (31%)	26/90 (29%)	7/57 (12%)	1/19 (5%)	10/37 (27%)	111/472 (24%)
Slope, *dL/mg/year*							
95 percentile	0.087	0.107	0.096	0.073	—	0.041	0.076
75 percentile	−0.003	0.009	0.007	−0.025	−0.023	0.002	−0.002
Median	−0.039	−0.016	−0.019	−0.062	−0.064	−0.014	−0.029
25 percentile	−0.091	−0.052	−0.054	−0.094	−0.167	−0.046	−0.080
5 percentile	−0.371	−0.523	−0.505	−0.243	−1.317	−0.235	−0.334

sion may be partially explained by the fact that the growth rate and size of the cysts are probably the main factors affecting progression in PKD patients with reduced GFR; in patients with other nephropathies, CRF progression may be due to more specific factors not necessarily related to the underlying disease, thus reducing the predictive value of the disease itself.

Another important finding of this study is the extreme variability in the rate of CRF progression. The greatest variability was observed in the CGN groups and may be explained by the fact that our "CGN" patients came from at least two subpopulations with a different slope and prognosis (see the distribution of CGN slopes in Fig. 1 and 2). Similar findings were obtained by the MDRD study [8] and that of Jungers et al [6], both of which found a considerably greater between-patient variability in the progression rate of CGN patients, whereas distribution was more homogeneous in those with PKD, CIN or vascular disease.

One limitation of our study may be the accuracy of diagnosis. Although the underlying renal disease was carefully assessed by means of a number of clinical, laboratory and radiological examinations in both studies, the diagnosis of HNS was often presumptive, and it is possible that some cases of renovascular disease or CGN may have passed unnoticed. Furthermore, the diagnosis of CIN was certainly overexpressed during the 1980s because ultrasonography was not widely available and renal biopsy was less used in clinical practice; this seems to be partially true in the case of the present analysis (there were more CIN patients in the NIC than in the AIPRI study).

Despite the relatively low progression rate observed in the NIC and AIPRI populations, we found that a good number of patients experienced a clinically relevant annual loss of renal function, whereas many maintained a relatively stable renal function or even had a positive slope partially regardless of treatment and baseline renal function (23% in the NIC and 24% in the AIPRI study). Interestingly, these percentage varied considerably according to the underlying renal disease, with the CIN and HNS groups displaying the highest proportion of patients with a positive slope and the PKD group having the lowest percentage. This is in line with the results of the MDRD study [8] showing that renal function was stable or improved during follow-up in 107/553 patients with moderate CRF (19%), and 27/219 with severe CFR (11%). The observation that CRF progression can spontaneously stabilize even for long periods is of particular importance because it could question the general belief that, after a certain degree of renal damage has been reached (the so-called "point of no return" [14]), and regardless of the cause, all CRF patients continue to lose renal function because renal failure itself may lead to maladaptive kidney alterations that give rise to a further loss of renal function. Given the highly variable natural history of renal disease, it also indicates that extreme caution is needed when evaluating the role of risk factors and treatment effect [15].

The results of the multivariate analyses of the NIC and AIPRI studies were different: age, the length of follow-up and PKD were found to be related to the slope of the reciprocal of S_{Cr} versus time in the NIC but not the AIPRI study, and baseline renal function and the standard error of the slope significantly correlated with the rate of CRF progression only in the AIPRI study. Proteinuria (baseline in the NIC and during follow-up in the AIPRI study) was negatively related to the rate of CRF progression in both studies, but a significant interaction between proteinuria and diastolic blood pressure during follow-up was only found in the AIPRI study. Systolic blood pressure was related to a faster progression rate in the NIC but not in the AIPRI study, probably because of the more intensive approach to blood pressure control adopted over

the last few years (the AIPRI patients were enrolled some years later than those in the NIC study).

It is important to underline that the models of multivariate analyses of the NIC and AIPRI studies predict, respectively, only 18% and 15% of the variation in the CRF progression rate, thus indicating that other unknown factors have a considerable effect on progression. The extreme variability observed in the rate of CRF progression in individual patients further stresses the complexity of the phenomena by suggesting the involvement of disease-specific pathogenetic factors rather than a single common mechanism of progression. In this light, future studies of the contributory role of genetic factors, as well as that of altered cytokine or growth factor production, should lead to a greater understanding of the other mechanisms involved in CRF.

In conclusion, this study of two large samples of CRF patients confirms that the underlying renal disease certainly plays a role in the natural history of chronic renal failure. However, the highly variable rates of CRF progression between the different diagnostic groups, as well as between the individuals with the same diagnosis, underline the fact that extreme caution is needed when assessing risk factors and predicting individual patient outcomes. Although this study offers a number of epidemiological insights into the behavior of chronic renal diseases, the need to put patients with different diseases in a single diagnosis group (CGN, but also CIN and PKD) and the unreliability of nonhistological diagnoses (often made in the case of many patients with HNS or CIN in everyday clinical practice) undoubtedly affected the results. Further studies of large but more homogenous samples are therefore needed to improve our understanding of the natural history of each nephropathy and lay the basis for the development of more specific therapeutic approaches.

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REFERENCES

1. El Nahas AM, Master-Thomas A, Brady SA, Farrington K, Wilkinson V, Hilson AJW, Varghese Z, Moorhead JF: Selective effect of low protein diets in chronic renal disease. *Br Med J* 289:1337–1341, 1984
2. Oldrizzi L, Rugiu C, Valvo E, Lupo A, Loschiavo C, Gammaro L, Tessitore N, Fabris A, Panzetta G, Maschio G: Progression of renal failure in patients with renal disease of diverse etiology on protein restricted diet. *Kidney Int* 27:553–557, 1985
3. Williams PS, Fass G, Bone JM: Renal pathology and proteinuria determine progression in untreated mild/moderate chronic renal failure. *Q J Med* 67:43–54, 1988
4. Stenvinkel P, Alverstrand A, Bergström J: Factors influencing progression in patients with chronic renal failure. *J Intern Med* 226:183–188, 1989
5. Wight JP, Salzano S, Brown CB, El Nahas AM: Natural history of chronic renal failure: a reappraisal. *Nephrol Dial Transplant* 7:379–383, 1992
6. Jungers P, Hannnedouche T, Itakura Y, Albouze G, Descamps-Latscha B, Man NK: Progression rate to end-stage renal failure in non-diabetic kidney diseases: a multivariate analysis of determinant factors. *Nephrol Dial Transplant* 10:1353–1360, 1995
7. Hannedouche T, Chauveau P, Kalou F, Albouze G, Lacour B, Jungers P: Factors affecting progression in advanced chronic renal failure. *Clin Nephrol* 39:312–320, 1993
8. Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, Rogers NL, Teshan PE and the Modification of Diet in Renal Disease Study Group: Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 51:1908–1919, 1997
9. Jovanovic DB, Djukanovic LD: Analysis of factors influencing chronic renal failure progression. *Renal Failure* 21:177–187, 1999
10. Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A: Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet* 337:1299–1304, 1991
11. Maschio G, Alberti D, Janin G, Locatelli F, Mann JFE, Motolese M, Ponticelli C, Ritz E, Zucchelli P and the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group: Effect of the Angiotensin-Converting-Enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334:939–945, 1996
12. Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A, Marcelli D, Francucci BM and the Northern Italian Cooperative Study Group: Factors affecting chronic renal failure progression: results from a multi-centre trial. *Miner Electrolyte Metab* 18:295–302, 1992
13. Locatelli F, Marcelli D, Comelli M, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A and the Northern Italian Cooperative Study Group: Proteinuria and blood pressure as causal components of progression to end-stage renal failure. *Nephrol Dial Transplant* 11:461–467, 1996
14. Maschio G, Oldrizzi L, Rugiu C: Is there a 'point of no return' in progressive renal disease? *J Am Soc Nephrol* 2:832–840, 1991
15. Locatelli F, Del Vecchio L, Andrulli S: REIN follow-up trial (letter). *Lancet* 352:2020–2021, 1998

Appendix 1. The variables included in the univariate analysis together with the slope of the reciprocal of S_{Cr} versus time

Variable	*P*-value NIC	*P*-value AIPRI
Stratum	0.001	0.001
Randomly allocated treatment	0.276	0.331
Age (years)	0.007	0.825
Gender (male/female)	0.276	0.223
Chronic glomerulonephritis (present/absent)	0.118	0.474
Nephroangiosclerosis (present/absent)	0.594	0.999
Chronic interstitial nephropathy (present/absent)	0.001	0.588
Polycystic kidney disease (present/absent)	0.002	0.576
Haemoglobin at baseline (g/dL)	0.343	0.688
Urinary protein excretion at baseline (g/day)	0.001	0.078
Urinary protein excretion during follow-up (g/day)	—	0.016
Length of follow-up (months)	0.001	0.001
Systolic blood pressure at baseline (mm Hg)	0.070	0.662
Diastolic blood pressure at baseline (mm Hg)	0.009	0.052
Mean blood pressure at baseline (mm Hg)	0.013	0.172
Systolic blood pressure during follow-up (mm Hg)	—	0.613
Diastolic blood pressure during follow-up (mm Hg)	—	0.031
Mean blood pressure during follow-up (mm Hg)	—	0.259
Standard error of the slope (dL/mg/month)	0.001	0.001